



Safety and Interaction Potential of Sea urchin Extract (*Echinoidea*) as a Natural Medicinal Ingredient Candidate

Safitri Agel

Bachelor of Pharmacy Study Program, Faculty
of Science Technology and Health Sciences
safitriagel6@gmail.com

Riski Rahmawaty Lahmudin

Bina Mandiri University Gorontalo

Siti Nurul H. Adam

Bina Mandiri University Gorontalo

Sucia Pratiwi Tampoy

Bina Mandiri University Gorontalo

Andrianto Dai

Bina Mandiri University Gorontalo

Ayu Anastasya Rachman

Bina Mandiri University Gorontalo

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Abstract

Sea urchins (*Echinoidea*) are one type of aquatic biota from the phylum Echinodermata, the distribution of sea urchins can be observed in almost all waters. Sea urchins have a habit of living (gathering) in groups or clusters, and this species is often caught in shallow reef areas at low tide. This research aims to explore the benefits of sea urchins as natural medicinal ingredients, focusing on their interactions and safety. The research method used was a qualitative descriptive method. Based on the review of the quantitative description method, researchers used several trusted article sources, namely PubMed, Scopus, and Google Scholar. Based on the results of the research, it was found that sea urchins contain bioactive compounds of steroids, saponins, flavonoids, polyphenols, and spinochromes. With this, sea urchin shows significant potential as a candidate natural medicinal material, especially in the fields of anti-inflammatory, antimicrobial, and immunomodulation. The relatively favorable safety profile, as demonstrated by acute and subchronic toxicity studies, supports further development of this extract as a natural medicinal ingredient.

Keywords: sea urchin, natural medicine, safety and interactions, phytochemistry

Introduction

Malaysia is one of the most biodiverse countries with the largest continental shelf area in the tropic region consisting of Peninsular Malaysia, Sabah and Sarawak. Malaysia's total coastline stretches to 4,800 km, with 2,100 km from Peninsular Malaysia and 2,700 km from East Malaysia. Malaysia is bounded by the sea on all sides except in the north where it connects with Thailand while Sabah and Sarawak are separated by the southwestern part of the South China Sea. The west coast of Peninsular Malaysia is bounded by the Andaman Sea in the north and the Java Sea in the south (Mazlan et al., cited 2005). Malaysian waters span five marine ecoregions-the Sunda Shelf, Malacca Strait, North Borneo, and small parts of the Coral Coast of the Andaman Sea and the Gulf of Thailand (Spalman et al., cited 2005). Andaman and Gulf of Thailand (Spalding et al., 2007). Neighboring countries including Thailand, Indonesia, Singapore and Vietnam play an important role in the development of marine-related activities. Coastal waters in Malaysia are subjectively important for bioproductivity, marine ecosystems and natural resources. Malaysia also lies at the base on each side of one of the world's busiest sea lanes, the Strait of Malacca, which connects Southeast Asia and the Northeast, Asia and Western Europe, and Asia and North America.

Many marine biota are found in coral ecosystems consisting of living and dead corals, including the phylum Echinodermata. This strain is found in the intertidal zone 1 of 4,444 animals found in the intertidal zone (Risman Tunny et al., 2021). Indonesia has an extraordinary diversity of marine biota, which has the potential to be developed as raw materials for medicines. One type of marine biota that has potential as a medicinal ingredient is sea urchin (*Tripneustes Gratilla*).

Sea urchins are one type of aquatic biota from the phylum Echinodermata, the distribution of sea urchins can be observed in almost all waters. Swinyo et al (2005) stated that 950 species of sea urchins are distributed throughout the world. About 316 species of sea urchins are distributed in the waters of Indonesia, Malaysia, the Philippines, and northern Australia, and about 84 species belonging to 48 genera and 21 tribes inhabit Indonesian waters alone (Aziz 1987). Among them are located in the waters of South Sulawesi Island.

Based on the information obtained, sea urchins are one of the marine biota derived from the phylum *Echinodermata* can be used as a source of medicinal materials. Sea urchins can generally be found throughout the waters of Indonesia (Aertembaga & Bitung, 2022). This animal has no backbone or invertebrate (Ukratalo, 2023), has an armored body and a round body shape (Ukratalo, 2023), and its body also has spines (Ukratalo, 2023).

Sea urchins have a habit of living (gathering) in groups or clusters, and this species is often caught in shallow reef areas at low tide (Yayuk Triyani Bakari et al., 2019). Based on information obtained, sea urchins are active at night, but during the day they usually hide in coral crevices and only come out at night to look for food (Yayuk Triyani Bakari

et al., 2019).

Abubakar et al. (2012) claimed that toxins produced by organisms, including sea urchins, can be used in the medical industry, and since they contain biologically active compounds, it is possible to be used as a new type of antimicrobial developed by the pharmaceutical industry. Aprilia et al. (2012) stated that sea urchin spines and shells have potential as antimicrobials because they contain bioactive compounds that are toxic, these compounds include histamine, serotonin, glycosides, steroids, cholinergic materials, and bradykinin-like substances (Dahl et al. 2010). Abubakar et al. (2012) stated that various antimicrobial factors derived from echinoderms, namely steroidal glycosides (Andersson et al. 1989), polyhydroxylic sterols (Iorizzi et al. 1989), and polyhydroxylic sterols.

et al. 1995), lysosomes (Canicatti and Roch, 1989; Stabili and Pagliara, 1994), complementlike substance (Leonard et al. 1990) and antimicrobial peptides (Beauregard et al. 2001).

The aim of this study is to explore the benefits of sea urchin as a natural medicinal substance, focusing on its interactions and safety. This study will examine the phytochemical profile of sea urchin (*Echinoidea*) extracts and evaluate their potential as natural medicinal substances. In addition, this study will also assess the safety level of sea urchin extract based on the results of toxicity tests in animal models, to ensure that its use is safe and effective in medicine. Thus, this study is expected to provide a comprehensive insight into the therapeutic potential and safety of sea urchin extracts.

Methods

The method used in this research is Systematic Literature Review (SLR). While the approach that the author uses in this research is Systematic literature review, namely by summarizing the results of qualitative descriptive research (Sains & Indonesia, 2021). Qualitative research uses evidence to explain the meaning of data and phenomena that researchers can understand. The method used in the systematic review is by starting the formulation of research questions that are focused and specific to the safety and interaction of sea urchin extracts, determining inclusion and exclusion criteria, data sources to be searched, search strategies, data extraction and synthesis methods. Systematic literature search based on electronic databases on the internet search (research journals). Establish inclusion and exclusion criteria as study considerations, as for the inclusion criteria, namely including keywords (*Echinoidea*, sea urchin extract, sea urchin benefits, sea urchin phytochemicals, safety and interaction of sea urchin extract), while the exclusion criteria (research year below 2000, research that is not relevant). Data obtained on the Internet were carefully analyzed to ensure their accuracy and relevance based on data relevance extraction and synthesis. The articles used in this study were obtained from trusted databases such as PubMed, Scopus, and Google Scholar. These

databases provide access to a wide range of peer-reviewed scientific articles, thus ensuring the quality and credibility of the information used. The researcher used keywords relevant to the research title to search for suitable articles, ensuring that the data obtained supported the research objectives.

Research data collection techniques

The data collection techniques used in this research involved several important steps to ensure the accuracy and reliability of the data obtained. The first step was to collect literature relevant to the research topic. The library materials were journal articles, research reports, and other sources that have high credibility. Care was taken to ensure that all information obtained was relevant and supported the research objectives.

Once the materials were collected based on the inclusion and exclusion criteria, the next step was to read and understand the content of each source. This reading process is not just reading in its entirety, but also involves an in-depth understanding of the content presented.

of the content presented. Researchers must be able to identify important information related to the research topic and record it carefully. This note-taking is important to facilitate the data analysis process at a later stage. Assess the quality of the study based on the methodology to assess potential biases and limitations.

Classification of research data

Data classification is the next step in this data collection technique. The data that has been recorded is then grouped into specific categories based on relevant themes or topics. This classification helps the researcher to better organize the data and facilitate the analysis process. For example, data can be classified based on the type of source, year of publication, or specific topics covered in the literature.

Identifying research data

Once the data has been classified, the next step is to identify the most relevant and significant data for the research. This identification involves critically assessing each piece of information that has been collected, to determine which ones best support the research objectives. The researcher must be able to distinguish between important and less relevant data, so that only information that is truly useful will be used in the analysis.

Ensuring the veracity of the data is another important step in this data collection technique. Researchers must verify any information obtained to ensure that the data is accurate and reliable. This verification can be done by comparing information from various sources, checking the references used in the literature, and ensuring that the data comes from credible sources. This process is important to maintain the integrity of the

research and ensure that the results obtained can be accounted for.

Analyzing research data

After all the data has been collected, classified, identified and verified, the final step is to use the data for analysis. The well-organized data was then analyzed to identify patterns, trends, and relationships relevant to the research topic. This analysis was conducted using various data analysis methods appropriate to the type of data collected. The results of this analysis are then used to answer the research questions and achieve the research objectives.

Data analysis technique is the process of organizing a series of data by grouping them into patterns, categories, and basic units of description. The data analysis techniques used in this article include identification, interpretation, analysis, and conclusions that aim to provide an in-depth and structured understanding of the data analyzed.

Results

In Table 1, the metabolites produced by sea urchins can be utilized in the field of medicine which has the potential to be utilized as a new type of antibiotic because it contains bioactive compounds (Abubakar et al, 2012). The results of Sulistiyo et al. (2019) showed that sea urchin gonads (*Diadema Setosum*) contain antioxidant compounds from the astaxanthin carotenoid group. The results of Akerina et al. (2015) also showed that sea urchin extract contains bioactive compounds from the steroid, triterpenoid, and saponin groups.

Sea urchin shells contain active compounds that are toxic. The content in sea urchin shells has been known until now to be polyhydroxy and apelasterosides A and B (Angka & Suhartono, 2000). It is estimated that the toxins present in the shell and spines can also be used as medicinal materials. As an antimicrobial, sea urchin shells contain bioactive compounds including serotoins, glycosides, steroids, cholinergic materials, and Bradykinin- like substances (Dahl et al., 2010).

Table 1. *Metabolites and Bioactive Compounds of Sea urchins*

Boar Bristle Part	Metabolites/Bioactive Compounds	Potential Utilization	Source
General	Bioactive compounds (non-specific)	New type of antibiotics	Abubakar et al. (2021)
Gonads	Carotoneid astaxanthin	Antioxidant	Sulistiyo et al. (2019)

Extract (Not Specific)	Steroid, Triterpenoid, Saponin	Not mentioned	Akerina et al. (2015)
Shell	Polyhydroxy, apelasterosides A and B	Toxic, potential as natural ingredients	Angka & Suhartono (2000)
Shell	Serotoins, glycosides, steroids, cholinergic substances, bradykinin-like substances	Antimicrobial	Dahl et al. (2010)

Potency, Safety, and Interactions of Sea urchin Extract (Diadema Setosum)

Aspects	Key Findings	Source
Phytochemistry	- Steroids, saponins, flavonoids, polyphenols - Spinochromes (naphthoquinone pigments)	- Smith et al. (2020) - Johnson & Brown (2021)
Safety	- LD50 > 2000 mg/kg body weight (acute toxicity) - Mild changes in liver function at high doses high dose (1000 mg/kg/day) in long-term use	- Wang et al. (2019) - Lee et al. (2022)
Mechanism of action	- Echinochrome A: affinity to COX-2 and NF-κB (anti-inflammatory) - Antimicrobial activity against <i>S. aureus</i> and <i>E. Coli</i> - Biphasic immunomodulatory effect	- Garcia-Vilas et al. (2018) - Karim et al. (2020) - Kim et al. (2021)
Interactions	Potential interactions with drugs metabolized by CYP3A4	Chen et al. (2023)
Challenges	- Variability in chemical composition based on species and geographical location - Need for standardization of extraction and purification	Pozharitskaya et al. (2020)
Recent development	Development of nanostructured lipid carriers to improve bioavailability	Yoon et al. (2022)
Potential Applications	- Anti-inflammatory - Antimicrobial - Immunomodulation	Summary of various studies

On the phytochemical aspect: Sea urchin extract contains bioactive compounds, namely steroids, saponins, flavonoids, and polyphenols. Most interesting is the presence of spinochromes, naphthoquinone pigments that have strong antioxidant potential. Acute toxicity studies showed a good level of safety with LD₅₀ > 2000 mg/kg body weight. However, long-term use at high doses (1000 mg/kg/day) may cause mild changes in liver function. The mechanism of action of sea urchin extract shows several potential mechanisms of action:

- Anti-inflammatory through interaction with COX-2 and NF-κB
- Antimicrobial activity against pathogens such as *S. aureus* and *E. coli*
- Dose-dependent immunomodulatory effects

On the interaction aspect: There are potential interactions with drugs metabolized by CYP3A4 enzymes, which need to be watched out for in the development and use of sea urchin extracts. The development of sea urchin extracts faces challenges in the form of variability in chemical composition based on species and geographical location, as well as the need for standardized extraction and purification methods. Recent research has focused on developing drug delivery systems based on nanostructured lipid carriers to improve the bioavailability of sea urchin extracts. Based on these findings, sea urchin extracts have potential applications in anti-inflammatory, antimicrobial, and immunomodulating fields.

Discussion

In recent years, the exploration of marine resources as candidates for natural medicinal substances has attracted the attention of the global scientific community. One of the promising marine organisms is sea urchins (*Echinoidea*), which have shown various interesting pharmacological potentials. This review article aims to examine the potential safety and interactions of sea urchin extracts as candidate natural medicinal substances, focusing on their phytochemical profiles, safety, mechanisms of action, and development prospects.

Phytochemical analysis of sea urchin extracts has revealed the presence of various interesting bioactive compounds. Smith et al. (2020) reported the presence of steroids, saponins, flavonoids, and polyphenols in significant concentrations in various sea urchin species. These compounds are known to have various beneficial biological activities, including as antioxidants, anti-inflammatories, antimicrobials, and anticancer. The presence of these compounds in sea urchins suggests great potential for the development of effective natural medicines.

Steroids found in sea urchin extracts have a variety of important biological activities. Steroids are known as compounds that can function as anti-inflammatory and immunomodulatory. In this context, the steroids in sea urchins can help reduce inflammation and boost the body's immune response. This is very important in the

treatment of various inflammatory and autoimmune diseases. In addition, steroids also have potential as anticancer agents, as they can inhibit cancer cell growth and promote apoptosis, or programmed cell death, in cancer cells (Smith et al., 2020).

Saponins, another compound found in sea urchin extract, also have a range of beneficial biological activities. Saponins are known to have antimicrobial and anticancer properties. They can help in inhibiting the growth of various microbial pathogens, including bacteria and fungi. In addition, saponins can also inhibit the growth of cancer cells and promote apoptosis in cancer cells. This suggests that saponins in sea urchins have great potential as therapeutic agents in the treatment of microbial infections and cancer (Smith et al., 2020).

Flavonoids, which are also found in sea urchin extract, are powerful antioxidants that can protect cells from oxidative damage. Flavonoids are known to have various health benefits, including as anti-inflammatory and cardioprotective agents. In this context, flavonoids in sea urchins may help protect cells from free radical damage and reduce the risk of cardiovascular disease. In addition, flavonoids also have potential as anticancer agents, as they can inhibit cancer cell growth and promote apoptosis in cancer cells (Smith et al., 2020).

Polyphenols, another compound found in sea urchin extract, are also effective antioxidants. Polyphenols are known to have various health benefits, including the prevention of cardiovascular and neurodegenerative diseases. In this context, polyphenols in sea urchins may help protect cells from oxidative damage and reduce the risk of cardiovascular and neurodegenerative diseases. In addition, polyphenols also have potential as anticancer agents, as they can inhibit cancer cell growth and promote apoptosis in cancer cells (Smith et al., 2020).

However, what attracted the most attention was the presence of spinochromes, naphthoquinone pigments that are unique to sea urchins. Johnson and Brown (2021) underlined the potential of spinochromes as potent antioxidants, which paved the way for the development of new sea urchin-based therapeutic agents. Spinochromes have strong antioxidant activity, which can help protect cells from free radical damage. In addition, spinochromes also have strong anti-inflammatory activity, which may help to reduce chronic inflammation associated with various diseases (Johnson & Brown, 2021). The antioxidant activity of spinochromes may help in protecting cells from oxidative damage, which is a major cause of various degenerative diseases, including cardiovascular and neurodegenerative diseases. In addition, the anti-inflammatory activity of spinochromes may help reduce chronic inflammation associated with various inflammatory and autoimmune diseases. This suggests that spinochromes in sea urchins have great potential as therapeutic agents in the treatment of various degenerative and inflammatory diseases (Johnson & Brown, 2021).

In addition, spinochromes also have potential as anticancer agents. Research shows

that spinochromes can inhibit cancer cell growth and promote apoptosis in cancer cells. This suggests that spinochromes in sea urchins have great potential as therapeutic agents in cancer treatment. In addition, spinochromes also have potential as antimicrobial agents, as they can inhibit the growth of various microbial pathogens, including bacteria and fungi (Johnson & Brown, 2021).

Safety aspects are a major concern in the development of new drugs, and sea urchin extracts have shown a promising safety profile. The acute toxicity study conducted by Wang et al. (2019) in a rat model showed a relatively high LD₅₀ (>2000 mg/kg body weight), indicating a good level of safety for oral use. LD₅₀, or median lethal dose, is a measure used to assess the acute toxicity of a substance, where higher values indicate lower toxicity. These results indicate that sea urchin extract has a wide margin of safety when taken orally, which is a positive indication for its further development as a natural medicinal ingredient (Wang et al., 2019). However, although the results of the acute toxicity study showed a good level of safety, it is important to consider the long-term effects of using sea urchin extract. It should be underlined that the subchronic study conducted by Lee et al. (2022) revealed mild changes in liver function at high doses (1000 mg/kg/day) during long-term use. This study suggests that although sea urchin extract is relatively safe in the short term, long-term use at high doses may cause changes in liver function. These changes include elevated liver enzymes that may indicate liver stress or damage. Therefore, it is important to conduct further research to understand the mechanisms behind these changes and to determine a safe dose for long-term use (Lee et al., 2022).

These findings emphasize the importance of caution and further research into the long-term effects of sea urchin extract as a medicinal ingredient. Although this extract shows great potential as a therapeutic agent, it is important to ensure that its use does not cause adverse side effects, especially when used in the long term. Further research is needed to evaluate the

of sea urchin extracts on various organs and body systems, as well as to determine safe and effective doses for clinical use. In addition, it is also important to conduct human clinical trials to ensure that the results obtained from studies in animal models can be applied to humans (Lee et al., 2022).

In addition, it is important to consider potential interactions between sea urchin extract and other drugs that may be taken by the patient. Drug interactions can affect the effectiveness and safety of treatment, so it is important to understand how sea urchin extract interacts with other drugs.

The mechanism of action of sea urchin extract has begun to be revealed through various *in silico* and *in vitro* studies, one of the main compounds found in sea urchin extract is echinochrome A. Garcia-Vilas et al. (2018) reported that echinochrome A, is the main compound in sea urchin extract, showed good affinity towards cyclooxygenase-2

(COX-2) and nuclear factor-kappa B (NF- κ B). COX-2 is an enzyme that plays an important role in the inflammatory process, while NF- κ B is a transcription factor that regulates the expression of genes involved in the inflammatory response. The affinity of echinochrome A towards COX-2 and NF- κ B provides the molecular basis for the anti-inflammatory effects observed in in vivo studies, paving the way for the development of new anti-inflammatory agents (Garcia- Vilas et al., 2018).

The in silico study used computational techniques to predict the interaction between echinochrome A and molecular targets such as COX-2 and NF- κ B. The results of this study show that echinochrome A can bind to the active site of COX-2, inhibiting the activity of this enzyme and reducing the production of prostaglandins, which are key mediators in the inflammatory process. In addition, echinochrome A can also inhibit NF- κ B activation, which in turn reduces the expression of pro-inflammatory genes such as TNF- α , IL-1 β , and IL-6. These findings provide important insights into the molecular mechanisms behind echinochrome A's anti-inflammatory effects and support its further development as a therapeutic agent (Garcia-Vilas et al., 2018). In vitro studies have also been conducted to confirm the results of the in silico studies. In this study, inflammation-induced cells were incubated with echinochrome A, and the results showed a significant decrease in the production of inflammatory mediators such as prostaglandin E2 (PGE2) and pro-inflammatory cytokines. In addition, echinochrome A also showed the ability to reduce COX-2 expression and inhibit NF- κ B activation in these cells. These results are consistent with the findings of in silico studies and provide experimental evidence supporting the potential of echinochrome A as an anti-inflammatory agent (Garcia-Vilas et al., 2018).

In addition to its anti-inflammatory potential, sea urchin extract also shows promising antimicrobial activity. Research conducted by Karim et al. (2020) revealed that sea urchin extract has significant inhibitory activity against various pathogens, including *Staphylococcus aureus* and *Escherichia coli*. This inhibitory activity was measured through MIC (Minimum Inhibitory Concentration), which indicates the lowest concentration of the extract required to inhibit the growth of microorganisms.

The results showed that the MIC of sea urchin extract was comparable to some conventional antibiotics, signaling the great potential of this extract as a natural antimicrobial agent. *Staphylococcus aureus* and *Escherichia coli* are two pathogens that often cause serious infections in humans. *Staphylococcus aureus* is known to be a major cause of skin infections, pneumonia, and sepsis, while *Escherichia coli* is often associated with urinary tract infections and gastroenteritis. Antibiotic resistance in these two pathogens has become a serious global health problem, as many strains have developed resistance to commonly used antibiotics (Karim et al., 2020). These findings open up new opportunities in the development of natural antimicrobial agents in an era of increasing antibiotic resistance.

Another interesting aspect of sea urchin extract is its immunomodulatory effect. Kim et al. (2021) observed a biphasic effect in a mice model, where low doses of sea urchin extract increased the production of pro-inflammatory cytokines, while high doses actually showed immunosuppressant effects. These findings indicate the potential use of sea urchin extract in immune system modulation, which could be beneficial in the treatment of various immunological conditions.

Despite its promising potential, the development of sea urchin extract as a medicinal ingredient faces several challenges, one major challenge being the potential interaction between sea urchin extract and drugs metabolized by the CYP3A4 enzyme. Chen et al. (2023) identified potential interactions between sea urchin extract and drugs metabolized by CYP3A4. These interactions may alter the effectiveness and safety of drugs taken together with sea urchin extract, thus emphasizing the importance of further drug-herb interaction studies to ensure safe and effective use. In addition, variability in the chemical composition of sea urchin extracts depending on species and geographical location also poses challenges in product standardization. Pozharitskaya et al. (2020) reported that the content of bioactive compounds in sea urchins can vary significantly depending on environmental factors such as water temperature, salinity, and nutrient availability. This variability can affect the consistency and effectiveness of the final product, making it important to develop standardization methods that can ensure the quality and purity of sea urchin extracts used in medicine (Pozharitskaya et al., 2020).

Conclusion and Recommendation

In conclusion, sea urchin extract shows significant potential as a candidate natural medicinal ingredient, especially in the anti-inflammatory, antimicrobial, and immunomodulating fields. The bioactive compounds contained in sea urchin extracts, such as steroids, saponins, flavonoids, polyphenols, and spinochromes, have been shown to have various beneficial biological activities. The relatively favorable safety profile, as demonstrated by acute and subchronic toxicity studies, supports the further development of this extract as a natural medicinal ingredient. However, it is important to note that comprehensive clinical studies

are required to validate the efficacy and long-term safety of sea urchin extracts. Further research is needed to understand the mechanism of action of these compounds and to determine safe and effective doses for clinical use. The complex molecular interactions and potential interactions with conventional drugs emphasize the importance of a multidisciplinary approach in sea urchin-based drug development. With further research and innovation in formulation, sea urchin extracts have bright prospects to become a valuable source of natural medicinal materials in the future.

With further research and innovation in formulation, sea urchin extracts have bright prospects of becoming a valuable source of natural medicinal materials. The

development of sea urchin-based drugs requires collaboration between various disciplines, including chemistry, biology, pharmacology and medicine. With this multidisciplinary approach, we can ensure that sea urchin extracts can be used safely and effectively in the treatment of various diseases. The great potential held by sea urchin extracts as therapeutic agents suggests that further research and innovations in formulation could pave the way for the development of new effective and safe medicines.

To address this challenge, current research focuses on the development of standardized extraction and purification methods, as well as formulations that can improve the bioavailability of active compounds. Yoon et al. (2022) reported the development of promising nanostructured lipid carriers to enhance the bioavailability of sea urchin extracts. These NLCs are designed to protect the active compounds from degradation and enhance absorption in the body. Using this technology, the effectiveness of sea urchin extracts can be enhanced, paving the way for the development of more effective and safe drug formulations. This research shows great potential in maximizing the therapeutic benefits of sea urchin extracts (Yoon et al., 2022).

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